Original Article

Evaluating the natural growth rate of metastatic cancer to the brain

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ABSTRACT

Background: Brain metastases are becoming increasingly more prevalent as cancer patients survive longer with both improved local and systemic therapy. Little is known, however, of the natural growth rates of brain metastases. This investigation aims to ascertain this growth rate of these lesions before the initiation of any CNS-directed therapy.

Methods: A total of 700 patients were screened, identifying 18 cancer patients (13 breast and 5 lung) with 29 brain metastases that were serially imaged from 2011 to 2017 before treatment for their intracranial metastases. Growth rates were measured by contouring lesions serially across at least two MRI studies in iPlan software by independent raters. These values were then compared between primary (breast and lung) cancer cohorts.

Results: The mean age at diagnosis was 53 and 95% were female. The interval between primary cancer diagnosis and brain metastases was 4.6 years and 1.2 years in the breast and lung cancer groups, respectively. Of the breast and lung cancer patients, 23% and 40% were deceased, with respective 5.08 cm³ and 2.44 cm³ initial tumor volumes. The average growth rate of lung and breast tumors was 0.018 and 0.040 cm³/day, respectively, with deceased patients having larger and faster growing tumors. Breast and lung metastases grew 2.39% and 1.14% of their total volumes daily and doubling times were 86 and 139 days, respectively.

Conclusion: This investigation provides a unique perspective into the biological growth of metastatic brain lesions. It is our hope that this study guides timing of treatment and informs both clinicians and patients of tumor growth kinetics before initiating treatment for intracranial metastases.

Keywords: Brain metastases, Breast cancer, Lung cancer, Metastatic growth, Tumor kinetics

INTRODUCTION

Over 170,000 patients develop metastatic brain tumors in the United States annually and 10–40% of the patients with malignant cancers develop brain metastases.[17,18,22,23] Between 12 and 20% of patients initially present with only brain metastases, significantly diminishing their survival compared to that of the primary cancer. Brain metastatic lesions are 10 times more common than primary brain tumors, with lung and breast cancers among the most common to spread to the brain.[10] A mean interval of 19.2 months is reported between primary cancer diagnosis and brain metastases identification, and without treatment, median survival may range between 1 and 3 months.[18] The implementation of adjuvant stereotactic radiosurgery has

prolonged median survival to 19.4 months.[1,6,9] Thus, early identification and judicious initiation of treatment may have a profound impact on patient survival.[17]

Despite the myriad reports that document growth rates of brain metastases after systemic chemotherapy and local radiotherapy, few have studied natural growth rates before the initiation of therapy.[24,25] A prospective trial delaying therapy in growing lesions would be unethical, however for various reasons, patients may undergo serial imaging studies with delayed treatment. This scenario, while rare, provides an opportunity to study the natural growth rates of metastatic lesions, unaltered by any anti-tumor treatments, as is the goal of the current study.

MATERIALS AND METHODS

The databases of both the Departments of Neurosurgery and Radiation Oncology at Montefiore Medical Center were mined to identify all patients with brain metastases from 2011 to 2017. From these patients, those who received at least two MRI studies before the initiation of radiation therapy or intracranial surgery were included in this analysis. All additional follow-up was also performed during this time period. Any subsequent imaging after intracranial treatment was not used, but follow-up was continued to determine mortality rates among these patients, even after treatment. Eighteen patients (having a total of 29 brain metastases) underwent successive MRIs before any form of intracranial treatment and were included in this study. Patient's medical records were reviewed for demographic, oncologic, radiographic, and treatment information. Permission was granted by the Albert Einstein College of Medicine Institutional Review Board to undertake this study.

To measure the growth rate of these tumors, Phillips 3T MRIs were loaded into iPlan software (Brain Lab, Munich, Bavaria), which is normally used at our institution to plan SRS treatments [Figure 1]. Within the software, tumors may be accurately contoured and volumetric data can be measured [Figure 2]. Each slice of the MRIs was individually contoured in all planes and each author contoured all tumors in the study in a blinded manner by a neurosurgeon and a radiologist. The agreement between ratings was measured to determine the reliability of the data. The growth rates were determined by dividing changes in tumors sizes with the time intervals between scans. A database was created in Excel (Microsoft Office Suite 2013) and statistical analyses were performed using SPSS software. Direct comparisons were performed to measure *P*-values for initial tumor size, growth rate, and doubling time among the two cohorts and between living and deceased patients, however, it was noted that the samples sizes were small given the nature of the report and unlikely to yield statistical significance between measurements.

RESULTS

Case selection and demographics

Of the 700 patients with lung and breast cancer presenting to the radiation oncology and neurosurgery services at a major New York medical center over the past 7 years, 154 were identified to have brain metastases (22%). Eighteen (having a total of 29 brain metastases) underwent successive MRIs before any form of intracranial treatment and were the few deemed eligible for inclusion in this study. Thirteen of these patients had primary breast cancer and five primary lung cancer. These patients represented 2.6% of all patients with lung and breast cancers and 12% of all patients with lung and breast cancer metastases. All but one patient was female (95% female) and the mean age was 53 years (range 28–81 years), with breast cancer patients representing the younger cohort, with a mean age of 47 versus 67 years. The average number of comorbidities per patient was 1.72, the most common being hypertension, hypercholesterolemia, and diabetes. About 25% of breast cancer patients had a family history of cancer and none of the lung cancer cohort. About 83% of patients presented with neurological symptoms, most commonly with headache, blurry vision, and nausea and vomiting. Major neurological symptoms including seizure, altered mental status, and hemiparesis occurred in 28% of patients. These symptoms were the impetus for obtaining imaging studies, with the remainder of patients undergoing surveillance imaging studies.

Only two of the 13 breast cancer patients were triple negative receptor bearers, and all lung cancer patients had nonsmall cell lung cancer lesions, with two EGFR positive. All were adenocarcinomas. One breast cancer patient had Stage I disease, two with Stage II disease, and 10 with Stage IV disease. The lung cancer patients presented with a wide range of initial stages, T1N1M0 disease in two patients, T2N2M0 in two other patients, and one patient with T3N3M1 disease. At the time of brain metastasis diagnosis, 61% of patients (77% breast and 20% lung) had metastases at other locations within the body, with the spine and liver being the most common sites. All patients underwent disease-specific primary cancer treatment including local surgical resection radiation therapy and non-CNS penetrating chemotherapy. At the time of review, five patients were deceased, 2/5 (40%) in the lung cancer group, and 3/13 (23%) of the breast cancer group [Table 1].

Tumor characteristics

The mean interval from primary lung cancer diagnosis to brain metastasis diagnosis was 1.17 years and 4.64 years in the breast cancer group. Patients had an average 1.6 lesions, with a range of 1–3 lesions in both primary cancer groups. The majority of which were supratentorial, with only 5/29
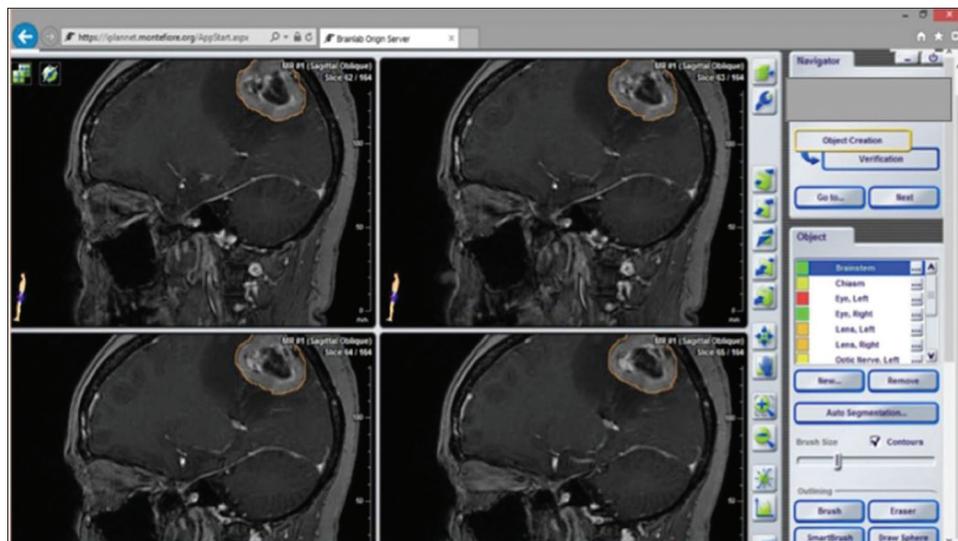
Figure 1: Plan software interface used to evaluate the volumes of the metastatic lesions.
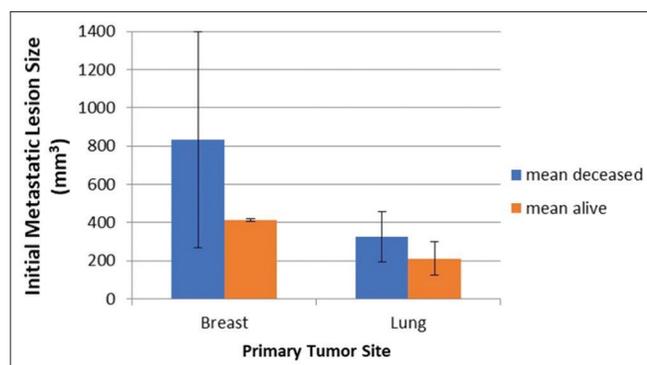

Figure 2: Initial tumor size, tumor type, and survival.

(17%) located in the posterior fossa, predominantly in the cerebellar hemispheres. The supratentorial lesions were evenly distributed throughout the cerebral lobes, with only two lesions being dural based. Four lesions were cystic (22%) and the majority (83%) had significant surrounding edema. The overwhelming majority of patients only had two serial MRIs before undergoing treatment or electing for hospice care.

Tumor size

The measurements of tumor volumes demonstrated inter-rater reliability of greater than 95% and this method improved on previously extrapolated measurements based on pixel recognition used in other studies in the past.[11] The mean volume of all lesions at the first time point was 4.45 cm³ (range 0.059 cm³–41.68 cm³, SD 9.04), 2.44 cm³ for the lung cohort, and 5.08 cm³ for the breast cohort, respectively ($P = 0.38$) [Figure 3]. Of the patients who were alive at the time of analysis, the mean metastasis volume was 3.67 cm³ compared to 6.87 cm³ in the patients who were

deceased ($P = 0.43$). The mean volume of living breast cancer patients was 4.13 cm³ compared to 8.34 cm³ in the deceased breast cancer patients, and 2.11 cm³ in the living lung cancer patients compared to 3.27 cm³ in those who were deceased.

The second MRI time point was on average 54.05 days after the first, with the scan interval significantly longer for the breast cancer cohort, 69.7 days, compared to 13.4 days for the lung cancer group. The mean scan interval was actually shorter for the deceased cohort compared to the living cohort, 35.4 and 61.23 days, respectively. The mean volumes at time point 2 were 2.61 cm³ and 8.27 cm³ in the lung and breast cohorts, respectively, and 6.26 cm³ and 8.93 cm³ in the living and deceased cohorts, respectively.

Tumor growth rate

The average growth velocity for all lesions was 0.034 cm³/d (34 mm³/d) and was significantly faster in the breast cancer cohort. The mean growth rate for lung cancer metastases was 0.018 cm³/d compared to 0.04 cm³/d in the breast cancer group ($P = 0.38$) [Figure 3]. The growth rate of lesions in the deceased patients was substantially faster than in the living cohort. Deceased patients had metastases that grew at 0.053 cm³/d compared to 0.023 cm³/d in the living group ($P = 0.19$). Among breast cancer patients, those that were deceased had the fastest growth rates, 0.08 cm³/d, compared to the living breast cancer patients at 0.03 cm³/d. The living lung cancer patients had the slowest growing tumors of all at 0.015 cm³/d compared to the deceased lung cancer patients at 0.025 cm³/d, who still had slower growing tumor than the living breast cancer patients. Due to faster growing tumors and long scan intervals, breast cancer patient on average had 2.78 cm³ of growth between scans, compared to 0.24 cm³ in the lung cancer group. The deceased patients had 1.86 cm³

Table 1: Demographic and tumor data between the study groups.

	Breast cancer (*n*=13)	Number	Lung cancer (*n*=5)	Number
Age, mean	47.40		67.40	
Gender	95%	12 1/3	5%	1/4
Family history	31%	4	0%	0
Comorbidities				
Hypertension	46%	6	60%	3
Diabetes	15%	2	40%	2
Obesity	8%	1	0%	0
COPD	0%	0	40%	2
Chronic kidney disease	0%	0	40%	2
Other systemic metastases	77%	10	20%	1
Neurologic deficit	85%	11	60%	3
ER+	62%	8	N/A	N/A
PR+	31%	4	N/A	N/A
Her2+	54%	7	N/A	N/A
EGFR+	N/A	N/A	40%	2
Deceased	23%	3	40%	2
Tumor location				
Frontal lobe	31%	4	40%	2
Temporal	23%	3	0%	0
Parietal	8%	1	80%	4
Occipital	23%	3	20%	1
Cerebellar	23%	3	0%	0
Supratentorial	54%	7	100%	5
Infratentorial	46%	6	0%	0
Metastatic brain surgery received			0%	0
Received chemotherapy	54%	7	80%	4
Cystic	31%	4	0%	0
Edematous	85%	11	80%	4
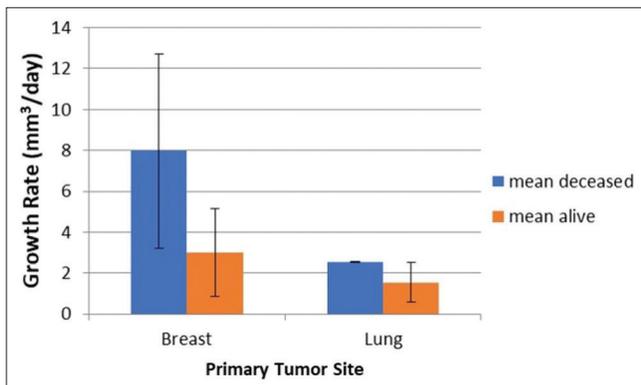
Figure 3: Tumor growth rate, tumor type, and survival.

of tumor growth between pretreatment scans, compared to 0.88 cm³ in the still living patients. In fact, each day, the breast cancer metastases grew 2.39% of their original tumor volumes. The lung cancer metastases grew more slowly but still at 1.15% of their initial volumes each day they remained untreated. Calculations for doubling time demonstrated that on average the breast cancer lesions doubled every 86 days, and the lung lesions doubled every 139 days ($P = 0.31$). The mean doubling time for the deceased patients was 105 days

and 98 days for the living patients, and neither was this comparison statistically significant between groups ($P = 0.91$).

The majority of patients were fortunate enough to be treated after this initial delay. All but three patients underwent radiation therapy and all lung cancer patients received radiation therapy exclusively. Only five patients underwent surgical resection of their metastases, primarily the larger breast cancer lesions. Of the 15 patients who were radiated, three underwent whole brain radiation and the remaining 12 received stereotactic radiosurgery to their lesions.

Cystic lesions

The initial size of the cystic lesions was significantly larger than the noncystic lesions, 20.45 cm³ compared to 1.96 cm³. Cystic lesions also expectedly grew faster at a rate of 0.2 cm³/d compared to 0.026 cm³/d in the noncystic growth. Finally, 40% of the deceased patients had cystic lesions, compared to only 20% in the surviving patients. All cystic lesions, as noted, were in the breast cancer cohort, and of the two patients with triple negative receptor metastases, one patient had two predominantly cystic lesion and the other did not have any.

Triple negative breast cancer lesions

Of the 22 breast cancer lesions, four were in two patients with confirmed triple negative receptor tumors. The four triple negative breast cancer tumors demonstrated smaller than average sizes at the first time point, 0.89 cm^3, yet some of the faster growing lesions of the cohort with growth velocities of 0.05 cm^3/d on average.

Reasons for delaying treatment

A number of reasons were identified to better understand why patients would delay their treatments. A few patients simply decided to undergo palliation with hospice care instead of aggressive treatment and may have delayed their decision-making while a repeat image was obtained. A couple patients, despite this diagnosis of metastases, were simply lost to follow up, albeit for a short period of time, only to return to clinic to have a repeat MRI performed. One patient refused surgery and treatment, only to return 1 month later to decide on a treatment modality. It is suspected that some patients may have had issues with scheduling treatment appointments, thereby delaying treatment for a short period, requiring reimaging. Two patients, while waiting for treatment developed new neurological symptoms, including a seizure and altered mental status, which resulted in repeat imaging before planned therapeutic management.

DISCUSSION

Of 20–50% of women who develop breast cancer metastases, 80% were reported in the past to die in the 1st year after diagnosis.[3] Fortunately, new therapeutics and treatment modalities such as stereotactic radiosurgery and microneurosurgery have significantly lengthened survival. SRS provides a form of less toxic, focused radiation compared to whole brain radiation therapy (WBRT) for metastases generally <3 cm and may show response in up to 79–90% of lesions.[9] Despite the effects of WBRT on the entire brain, which include inflammation and negative neurocognitive effects, it is still used for palliative treatment of large and innumerable metastases.[1,6] SRS is optimal for areas of high eloquence, small localized tumors, and those not reachable by surgery. Tumors greater than 3 cm treated with SRS are correlated with limited local control rates and are, therefore, not treated solely with this radiation type.[5] Therefore, growth data in our report may provide meaningful information in regards to treatment timing, as lesions approach this 3 cm mark. In addition, our work based on three-dimensional modeling and volumetric analyses takes much more precise measurements of the overall lesional impact on surrounding brain tissue, in a manner that may have much greater clinical relevance than antiquated two-dimensional measurements. In the future, as volumetric analyses become more commonly used, it may be of value to determine volume cutoffs for radiation therapy, rather than single plane measurements that are currently being employed.

The overall expectation for survival is 1–2 months for untreated metastatic patients and 4–6 months for timely treated patients.[1,2,5,7,9] Therefore, understanding the natural growth rates of these lesions set the foundation for understanding the time frame in which treatments should be initiated and may form a template for the patient's survival expectancy.

Patient and tumor characteristics

It is rare that a patient will be diagnosed with a new brain metastasis and not undergo treatment shortly thereafter. Treatment should begin right after diagnosis, and the purpose of this study was to demonstrate the risk of delaying treatment. In our large cohort of 700 patients with metastases, serial imaging in untreated patients occurred only a handful of times. From these rare cases, we studied the uninhibited growths of these tumors.

As expected in a cohort of predominantly breast and lung cancer patients, most were women, in their 4th and 5th decades of life, similar to demographics found in the literature.[11,14] Comorbidities and symptomatic presentations (commonly headaches and seizures) were typical for this population.[2] Interestingly, most of the breast cancer patients had other metastases at the time of brain metastases diagnosis, but 80% of lung cancer patients did not. The data support that lung cancer is more exclusively spread to the brain, possibly due to circulatory flow of hematogenous metastases. Survival rates between the lung and breast cancers as demonstrated in this study are consistent with those reported in the literature.

This study demonstrated the mean interval from primary lung cancer diagnosis to brain metastasis was 1.17 years and 4.64 years in the breast cancer group. This is slightly longer than the average time of diagnosis of breast cancer to brain metastasis previously reported of 34 months (2.83 years). This value is unfortunately not standardized and usually reliant on clinical suspicion alone.[4] The current lung data are much more consistent with the previously reported median time of diagnosis of 400 days or 1.10 years after primary tumor identification.[24] Expectedly, the deceased patients had larger initial tumor sizes, which likely took longer to be identified and treated.

Tumor size and growth

In this study, we demonstrated that lung cancer metastases grew at the same rate as a previously demonstrated in an independent prospective study.[24] This helps validate previously reported data and the potential to use this data to reliably guide therapy in the future. Surprisingly, we

demonstrated that breast cancer metastases grew significantly faster than lung cancer metastases, related to tumor biology but also contributed by cystic fluid production. Since these breast and lung tumors have such different biological characteristics, it is expected that they will grow at different rates and have different degree of cyst production in the brain. Therefore, different time courses may guide the growth and treatment of these different metastases.

Natural growth may be vitally important to determine prognostic factors for the overall survival of patients, however, the strict correlation between tumor size and survival is unclear and is likely a multifaceted process in which many systemic factors may play a role.[9] In addition to prognostic factors, determining the natural growth rates of these lesions can help identify key milestones in tumor growth, such as the doubling time, as well as the time to a size no longer amenable to focused radiosurgery.

The positive effect of diagnosing metastases early is demonstrated in Park *et al.* Patients that underwent early pretreatment MRIs had a significantly higher 5-year survival rate, compared to those who did not undergo pretreatment MRIs.[16] Serres *et al.* have demonstrated a possible way to detect metastases earlier, with the imaging of vascular cell adhesion molecule-1 (VCAM-1), through iron oxide microparticles used as an MRI contrast agent. This diagnostic tool is aimed at the early detection of metastases and could improve treatments and provide options for new types of therapeutics.[19] Understanding the growth rates of these lesions could help validate the application of these advanced imaging modalities in the future, as they enter clinical practice.

The natural growth rate of nonsmall cell lung cancer found by Yoo *et al.* which demonstrated the feasibility of the approach taken in this study was 0.01 cm^3/day, similar to the 0.018 cm^3/day rate obtained in the present cohort of lung cancer patients.[24,25] The previous study had been conducted after all the tumors development of chemoresistance, which was assumed to be similar to natural growth. Since our population was completely untreated, they may have had a slightly faster growth rate.

There was a notable difference in the growth rates of the breast and lung cancer patients. Therefore, biology may play a major role in tumor growth and patient survival. However, the deceased patients did have greater than twice as fast growth of tumors when combining both groups, suggesting that tumor growth in itself, despite tumor type, was in fact relevant to survival. These data suggest that prognosis is dependent on several potentially independent factors.

The average initial lesion size in the Yoo study was 0.04 cm^3 compared to 2.44 cm^3 in this study, with Yoo's cohort being previously treated. Despite the smaller tumor size, the velocities between our studies were essentially equal. Therefore, while their study may have imaged these metastases earlier or after initial treatment response, it is reassuring that the tumors appear to maintain the same growth rate throughout their existence. In addition, based on the pooled data between these studies, it is suggested that the growth rate may be linear, however, a stepwise or even logarithmic growth rate may also still be possible. Few studies have addressed this question in the literature however in a review of 22 studies involving 675 patients, the data demonstrated that growth rates of primary intracranial tumors were linear.[15,20] We may utilize these data to suggest that metastatic lesions may grow in a linear rate as well. More imaging data need to be obtained to determine the growth rate at multiple time points to help answer this question in the future.

An interesting finding in our study was that each day, breast cancer tumors grew 2.39% of the initially identified tumor size, and the lung cancers, 1.15% of their initial sizes. This also demonstrated that tumor doubling time was 86 days for breast cancers and 139 days for lung cancers. This was consistent with other studies that showed tumor doubling time of under 100 days for up to 1/3 of lung cancers and 40% double time between 100 and 400 days.[12] Others have also noted that lesions may double in size over the course of only 1 month or less, consistent with 6 of our breast cancer patient's tumors.[21] Yoo *et al.* who looked at percent growth in lung cancer brain metastases found similar growth of 1.67% of tumor volume of lung metastases per day. Presenting this data during initial consultation could certainly concern patients who are scheduled for treatment far into the future. Weeks or months of waiting certainly are enough time for substantial tumor growth to occur and may compromise effective therapeutic control of these lesions. We concluded that treatment should not at all be delayed, when feasible.

Cystic tumors

Cystic tumors in this study were larger and grew faster than noncystic lesions. This can certainly be explained by the addition of the cystic cavity in the overall size of the lesions and the likelihood that cystic fluid production occurs at a faster rate than growth of solid tumor mass. Interestingly, 50% of the deceased patients had cystic lesions, compared to 20% mortality in the noncystic lesions. Mortality may have been directly linked to tumor size, but also tumor biology. Even without the consideration of these cystic lesions in the breast cancer group, the breast tumors grew faster and had larger initial sizes than the lung cancer group.

Triple negative breast cancer

Triple negative tumors have worse prognostic outcomes than other breast cancer types with a mean survival between

3.4 and 4.9 months after diagnosis.[13] In this report, these lesions had smaller initial sizes but faster growth velocities than a majority of the other tumors. While triple negative tumors portend a worse prognosis to patients, it may not necessarily be related to their growth rates, but simply to their resistance to therapeutics that may be effective in other tumor subtypes.[8]

Treatment delays

Reasons for treatment delays varied and included election to not be treated, decision to undergo hospice care, failure of the patient to follow-up, scheduling delays, and finally, patients needing to take time to make a decision on treatment choice. Some of these delays were preventable by having doctors thoroughly explain the need for prompt treatment due to tumor growth to their patients. All attempts should have been made to contact patients lost to follow up, and treatment initiated as soon as possible. Of course, all of these issues and patient desires must be balanced in a system that is equitable to all, for both the individual and for the society.

Limitations

The limited number of patients, due to the criteria of the study, weakens the statistical strength of the data. Larger cohorts of data may in the future demonstrate significance in a number of measures in our study that were approaching significance. While the lesions had to be manually contoured, using multiple blinded raters demonstrated a greater than 95% inter-rater reliability, error in true volumetric measurements may have occurred. Older, less clear images, and tumor edema may have contributed to imprecise contouring of lesions. It is possible that patients with metastases who refused all treatments and never presented to either the radiation oncology nor neurosurgery services would have been missed in this analysis. The cystic growth of lesions could have skewed the breast data; however, this is legitimate and significant volumetric information, contributing to intracranial mass effect. Breast lesions were still larger and faster growing despite these lesions. The patient charts may have been incomplete and there could have been additional deceased patients in our cohort, although each patient had notes written within 3 months of this report. Despite these limitations, the authors feel that the data are meaningful and may inform patient care in the future.

CONCLUSION

The data presented in this report demonstrate that metastatic tumors to the brain grow at substantial rates per day, calling into action patients and clinicians to not delay treatment for these lesions, whenever possible. These data have previous

not been reported in the literature and have elucidated reason at least in our cohort as to why delays have occurred in the past. Further studies should evaluate tumor growth in more than 2 serial pretreatment scans to confirm whether growth of these lesions is linear, exponential, or stepwise, as well as study much larger cohorts of patients to determine the statistical significance of growth rates between patients and tumor types. In addition, other types of metastases may be evaluated and prospective trials may be conducted to evaluate whether outcomes improve in patients who are hyperacutely treated, compared to those who undergo standard treatment regimens.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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